

- II. Claims 3-14, drawn to a crystalline polypeptide-ligand complex, classified in class 530, subclasses 300 and 350.
- III. Claims 15-20, drawn to a method for determining the three-dimensional structure of first polypeptide comprising the catalytic domain of a Tie-2 protein, classified in class 702, subclass 27.
- IV. Claims 21-35, drawn to a method of identifying an inhibitor compound of a Tie-2 protein, classified in classes 702 and 435, subclasses 19 and 7.1 respectively.
- V. Claims 36-58, drawn to a method of identifying a potential inhibitor of a Tie-2 protein, classified in class 702, subclass 19.
- VI. Claims 59-75, drawn to a Tie-2 inhibitor, classified in class 514, subclass 1.
- VII. Claims 76-83, drawn to a method of treating a Tie-2 dependent condition in a patient, classified in class 514, subclass 2.
- VIII. Claim 84, drawn to a method of decreasing fertility in a patient, classified in class 514, subclass 1.
- IX. Claims 85-86, drawn to a method of promoting angiogenesis or vasculogenesis in a patient, classified in class 514, subclass 1.
- X. Claim 87, drawn to a method of determining the three-dimensional structure of a polypeptide containing the catalytic domain of Tie-2 protein, classified in class 702, subclass 19.

If Groups II and IV are chosen, the examiner has required a specific ligand structure to be used for the initial examination of the instant application.

If Group V is chosen, the Examiner has required a specific set of crystal structural coordinates (such as one from Figures 3 through 6) to be used for the initial examination of the application.

If Groups VI-IX are chosen, the Examiner has required a specific Tie-2 inhibitor and specifically listing the 2 or more characteristics listed in (a) – (t) in claim 59 to be used in the initial examination of the instant application.

The Examiner has also required election of a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. Applicants respectfully traverse the restriction and election requirements. However, to be fully responsive to the restriction and election requirements, Applicants provisionally elect Group IV and the species of Inhibitor III that is on page 13 of the instant specification with traverse. Claims 21-27 and 32-33 read upon the provisionally elected species.

Applicants respectfully traverse the restriction requirement. The Examiner alleges that inventions of Groupings [I-V and X] and [VI-IX] of the instant Office Action are independent inventions because they are directed to different chemical and entity types regarding the critical limitations therein. The Examiner states that the critical feature for Groups I-V and X is a crystalline polypeptide and that for Groups VI-IX the critical feature is a Tie-2 inhibitor. The Examiner asserts that the instant application contains patentably distinct inventions that require separate searches that would place a serious burden on the Examiner.

Proper restriction between independent and distinct inventions claimed in the same application requires that (1) the invention must be independent and distinct as claimed and (2) there must be a serious burden placed on the Examiner by not requiring restriction. If either criteria is not met, restriction is not proper.

With respect to the term “independent”, “independent” means that there is no disclosed relationship between the two or more subjects disclosed in a patent application. M.P.E.P. §802.01. The instant application is directed to a method of identifying inhibitors of Tie-2. Specifically, the invention relates to a polypeptide which comprises the catalytic domain of Tie-2, a crystalline form of this polypeptide and the use of structural information derived from the crystalline polypeptide for designing and/or identifying potential inhibitors of Tie-2 which can be used to treat conditions associated with Tie-2. These components of the invention are connected

in that the design of potential inhibitors of Tie-2 is based upon the structural information obtained from the crystalline form of the polypeptide. Therefore, the subjects of the instant application are not "independent" as determined by M.P.E.P. 802.01.

The term "distinct", as defined in M.P.E.P. § 802.01, means two or more subjects as disclosed are capable of separate manufacture, use or sale as claimed, and are patentable over each other. In the instant application, the invention is directed to methods of identifying inhibitor of Tie-2. The identification of such inhibitors is comprised of a series of steps (obtaining the polypeptide, obtaining the crystalline form of the polypeptide, analyzing the structure of said crystalline form), each of which is dependent upon successfully completing the prior step. For example, one cannot obtain crystal structure coordinates without first obtaining the crystal structure. Therefore, the use of one subject, e.g. obtaining crystal structure coordinates, is irrefutably connected with, that is, not separate from, another subject, e.g. obtaining the crystal structure. Thus, the subjects disclosed in the instant application do not meet the criteria for "distinct" as defined in M.P.E.P. § 802.01.

Thus, Applicants respectfully submit that the instant invention does not meet the threshold of "two or more independent and distinct" inventions as required in 35 U.S.C. §121 and as such the restriction requirement is improper.

If the Examiner maintains the restriction requirement, the Examiner should at the very least group the claims as follows. Groups I and II should be combined into one group. Groups III, IV, V and X should be combined into one group. Groups VI, VII, VIII and IX should be combined into one group.

With respect to the burden of the examination, M.P.E.P. §803 states:

If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent and distinct inventions.

Applicants respectfully request that Group I, class 530, subclass 350 and Group II, class 530, subclasses 300 and 350 be combined into a single group. Claims 1-2 and 88 read upon Group I and claims 3-14 read upon Group II. These groups are directed to a crystalline polypeptide and a crystalline polypeptide-ligand complex. These groups share the class 530 and subclass 350. As acknowledged by the Examiner the critical feature of Groups I and II is a

crystalline polypeptide. Thus, Applicants submit that the Examiner could search and examine Groups I and II without serious burden.

Applicants respectfully request that Group III, class 702, subclass 27, Group IV, classes 702 and 435, subclasses 19 and 17.1, respectively, and Group V, class 702, subclass 19, be combined into a single group. Claims 15-20 read upon Group III, claims 12-35 read upon Group IV. Claims 36-58 and the crystal structural coordinates from Figure 5 read upon Group V. Groups IV and V are drawn to a method of identifying TIE-2 inhibitors. Group III is drawn to a method of determining the three dimensional structure of a first polypeptide. Additionally, all three groups share class 702 and subclass 19. As acknowledged by the Examiner the critical feature of groups III, IV and V is a crystalline polypeptide. Thus, Applicants submit that the Examiner could search and examine Groups III, IV and V without serious burden.

Applicants respectfully request that Group VI, class 514, subclass 1, Group VII, classes 514, subclass 2, Group VIII, class 514, subclass 1, and Group IX, class 514, subclass 1, be combined into a single group. Claims 59-75 read upon Group VI, claims 76-83 read upon Group VII. Claim 84 reads upon Group VIII and claims 85-86 read upon Group IX. Groups VI, VII, VIII and IX are drawn to a Tie-2 inhibitor and methods of treating TIE-2 dependent conditions. Additionally, all four groups share class 514 and three of these groups also share subclass 1. As acknowledged by the Examiner the critical feature of groups VI, VII, VIII and IX is a Tie-2 inhibitor. Thus, Applicants submit that the Examiner could search and examine Groups VI, VII, VIII and IX without serious burden.

Based upon the foregoing, the restriction requirement should be withdrawn and all of the subject matter of claims 1-88 should be prosecuted together, or at least that Groups IV, V and X be combined into one group and claims 21-58 be prosecuted together. Prompt and favorable action is earnestly solicited.

If the Examiner believes that there are any issues that could be resolved in a telephone conference, Applicants invite the Examiner to call Applicants' undersigned agent.

Respectfully submitted,

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